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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/778,388	02/07/2001	Francis C. Szoka JR.	13054.01600	4514

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/778,388	Szoka et al
Examiner	**Art Unit**
Richard Schnizer	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 23, 2002* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 5-7, and 10-52* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 5, 7, 10-13, 15, and 19-52* is/are rejected.

7) ☒ Claim(s) *6, 14, and 16-18* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Feb 7, 2001* is/are a) ☒ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered as Paper No. 8 on 12/23/02.

Claims 3, 4, 8, and 9 were canceled as requested.

Claims 1, 2, 5-7, and 10-52 remain pending and are under consideration in this Office Action.

Rejections/Objections Withdrawn

1. The objections to claims 22, 23 and 38-47 over acronyms are withdrawn in view of Applicant's amendments.

The rejection of claims 38-41 and 50-52 under 35 U.S.C. 112, first paragraph is withdrawn in view of Applicant's amendments.

The rejection of claims 12, 33, 38-47, 50-52 under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendments.

The rejections of claims 1, 2, 5-7, 11-13, 15, 16, 19-21, 24-36, 38, 39, 42, and 50-52 under 35 USC 102 are withdrawn in view of Applicant's amendments.

The rejections of claims 1-3, 41, 48, and 49 under 35 USC 103 are withdrawn in view of Applicant's amendments.

Claim Objections

2. Claims 6, 14, and 16-18 are objected to because they depend from rejected base claims, but would be allowable if rewritten in independent form including all the limitations of the base claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 12 and 19-52 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 12 was amended to include the term "double ortho ester". Applicant has not pointed to specific support in the specification for this term, and none is apparent, so it represents new matter.

In order to overcome an art of certain claims rejection based on Nantz (US Patent 6,200,599) claims 19-52 were amended to contain a limitation requiring that hydrolysis of an ortho ester "directly detaches" a hydrophilic portion of a composition from a hydrophobic portion. Applicant asserts at page 10 of the response that, in the composition of Nantz, hydrolysis of the ortho ester does not directly lead to release of the hydrophilic portion, and

instead a second intramolecular transesterification is required for release of the hydrophilic portion. Applicant fails to point to any passage in the instant specification that supports release of the hydrophilic portion as a direct consequence of ortho ester hydrolysis without any subsequent intramolecular reactions. Instead, Applicant relies on a document published after the filing date of the instant application (Guo et al (2001) which asserts that one subgenus of diortho esters inherently has this characteristic. However, the claims are not limited to this subgenus which is shown in instant Fig. 1. The claims are broader and embrace ortho ester compounds as well. Because there is no apparent support in the specification for limiting the claims to the genus of all ortho ester compounds that release a hydrophilic moiety as a direct result of hydrolysis, while eliminating the subgenus of ortho ester compounds that require a further intramolecular reaction, the amended claims contain new matter. It is suggested that Applicant should incorporate into the claims the structure of the diortho ester that represents the genus of compounds having the required characteristics.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is indefinite because it is unclear what is intended by "double ortho ester". This term is not defined in the specification, and a search of the Medline and WEST databases retrieved zero hits, suggesting that it is not a term of art. It is unclear to the Examiner what is the distinction between a "diortho ester" and a "double ortho ester", so it is not clear that claim 12 further limits claim 11.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1, 2, 7, 10, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Klaveness et al (US Patent 6,106,806, issued 8/22/00).

Klaveness teaches ultrasound contrast agents that are vesicular in nature and composed of polymerizable or crosslinkable units of the general formula $[(X)_p(R^{10})_q]B$, wherein X is a hydrophilic group, R^{10} is a hydrophobic group, and B is a crosslinker. See abstract; column 6, lines 1-20; and column 6, line 62 to column 7, line 7. Additional groups $[(X)_p(R^{10})_q]B$ may be

crosslinked to a polymer of groups $[(X)_p(R^{10})_q]B$. The hydrophilic group may be a polyethylene glycol and may comprise a cationic quaternary amine. See column 6, lines 52-61, and column 7, lines 27-29, and column 14, lines 7-14. The hydrophobic group may be for example, cholesterol, acylphosphatidylserine, or acylphosphatidylcholine. See column 7, lines 7-14. The crosslinker may be an ortho ester. See column 6, lines 48-51. Formation of ortho ester crosslinks between these groups would necessarily result in compounds in which hydrophilic groups can be separated from hydrophobic groups by acid hydrolysis of an ortho ester.

Thus Klaveness anticipates the claims.

6. Claims 1, 2, 5, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Harris (US Patent 6,258,551, issued 7/0/01), as evidenced by (Voet et al, in Biochemistry, Second Edition, John Wiley and Sons, 1995) .

Harris teaches compositions in which polyethylene glycol (PEG) is conjugated to phospholipids, and these PEG moieties are crosslinked by ortho ester linkages (see column 3, lines 36-40 and 59-65). The molecular weight of the PEG may be 300 (see claim 18 at column 12). Formation of ortho ester crosslinks between these groups results in compounds in which one PEG-phospholipid conjugate can be separated from another by ortho ester hydrolysis. This necessarily results in separation of a hydrophobic group (the phospholipid of one conjugate) from a hydrophilic group (the PEG of another conjugate).

Thus Harris anticipates the claims.

It is noted that the term "phospholipid" in Harris is recognized in the art to refer to a subgenus of diacylglycerols. See Voet, page 28, column 2, first paragraph, and Figure 11-4 on page 281 which discloses the general structure of phospholipids showing that they are diacylglycerols.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 1, 2, 11-13, 19, 30-33, 38, and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sparer et al (US patent 5,211,951, issued 5/18/93), in view of Mohr et al (BIOCHIMICA ET BIOPHYSICA ACTA, (1992 Jun 26) 1126 (3) 247-54).

Sparer teaches compositions comprising bioerodable poly(ortho esters) and beneficial agents. The ortho esters may be 3,9-bis-(ethylidene)-2,4,8,10-tetraoxaspiro [5,5] undecane. See e.g. claim 9. The beneficial agent may any beneficial agent with two or more hydroxyl groups (see column 3, lines 2-5). The ortho esters may link the beneficial agents to polyethylene glycol. See column 7, lines 12-17. Pertinent to claim 19, the composition can be thought of as an encapsulator because it functions as an implant comprising the crosslinked PEG and beneficial

agent. Pertinent to claims 38 and 39, the intended use of the composition is to deliver drugs to cells by implantation, followed by hydrolysis of the ortho ester linkers. See abstract, column 1, lines 50-60 and column 2, lines 3-5.

Mohr teaches that ubiquonone (the reduced from of coenzyme Q, comprising two hydroxyl groups) is a potent antioxidant present in LDL and that dietary administration of coenzyme Q increased concentrations of ubiquinone in plasma and lipoproteins, thereby increasing resistance of LDL to radical oxidation.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer ubiquinone in vivo by the method of Sparer, i.e. by a linking ubiquinone to PEG by a 3,9-bis-(ethylidene)-2,4,8,10-tetraoxaspiro [5,5] undecane ortho ester cross linker. One would ave been motivated to do so because Sparer teaches that any beneficial agent with two or more hydroxyl groups can be used in the invention, and because ubiquinone is clearly a beneficial agent, according to Mohr. Further, the resulting composition would provide controlled-release dosage of ubiquinone, obviating the need for dietary supplementation.

Thus the invention as a whole was prima facie obvious.

Claims 30-33 are included in this rejection because the composition of Sparer appears to be substantially identical to that claimed. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). The office does not have the facilities for examining and comparing applicant's product with the product of the

prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Summary

Claims 12 and 19-52 introduce new matter into the disclosure.

Claims 1, 2, 5, 7, 10, and 15 are anticipated.

Claims 1, 2, 11-13, 19, 30-33, 38, and 39 are obvious.

Conclusion

No claim is allowed. Claims 6, 14, and 16-18 are objected to because they depend from rejected base claims, but would be allowable if rewritten in independent form including all the limitations of the base claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JEFFREY SIEW
PRIMARY EXAMINER
3/5/03